



The Potential Association of Human Leukocyte Antigen (HLA)-A and -B with COVID-19 Mortality: A Neglected Risk Factor

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Dear Editor-in-Chief

To date, six types of coronaviruses have been detected, of which only two have triggered epidemics with high death rates; severe acute respiratory syndrome (SARS-CoV) and the Middle East respiratory syndrome (MERS-CoV). Nevertheless, the novel coronavirus disease pneumonia (COVID-19 or SARS-CoV-2) virus was introduced in 2019 seven years after the MERS epidemic, rapidly triggering a worldwide outbreak (1). This emerging pneumonia was first identified in Dec 2019 from Wuhan, the capital of Hubei province in China in Dec 2019 (2). Patients infected with this novel COVID-19 virus have severe pneumonia signs like fever, tiredness, dry cough and acute respiratory distress (1).

The human leukocyte antigen (HLA) has been correlated with many various diseases, in which the profile of these alleles varies significantly between different populations throughout the diseased persons (3). Therefore it is significant to evaluate the relationship between different HLA alleles and disease among various racial groups (3). Thus, the main objective of this study was to determine the relationship between HLA-A and -B with COVID-19 mortality in Iran.

Our study was performed on 20 random blood samples of dead cases infected with COVID-19 and the prevalence of major histocompatibility complex (MHC) class I (-A, -B) alleles were determined for each sample. Among the samples,

the HLA-A and -B antigens were determined by Single Specific Primer (SSP) PCR. Control information was collected from a published study, which recruited a sample of 500 controls from healthy people in northeastern Iran (4). Eventually, the Chi-square test was applied to analyze the statistical significance between HLA-A and -B alleles and control groups. The significance level was defined to be less than 0.05 (P -value < 0.05). The main features related to the distribution of HLA-A and -B alleles between the patients and control groups are shown in Table 1. Of HLA-A alleles, the most common subtypes were HLAA*01 and HLA-A*02 among patients and healthy controls, respectively. Among the patients with HLA-A alleles, HLA-A*01 (P -value < 0.001) and HLA-A*03 (P -value = 0.003) had the highest association with the COVID-19 and were associated with an increased risk of mortality. Also, of HLA-B alleles, the most common subtypes were HLA-B*07 and HLA-B*35 among patients and healthy controls, respectively. Among the patients with HLA-B alleles, the HLA-B*07 (P -value < 0.001) and HLA-B*38 (P -value = 0.006) had the highest association with the COVID-19 and were associated with an increased risk of mortality. Multiple surveys have shown that there is a statistically significant influence of specific HLA alleles and some diseases.



Table 1: Allele frequency of class I HLA-A and -B in dead cases of COVID-19 (our study) in comparison to total Iranian population

Variable	Patient's alleles (n = 20)	Control's alleles (n = 500)	χ^2	P-value
HLA-A				
HLA-A*01	50%	11.5%	23.290	<0.001
HLA-A*02	10%	20.9%	3.903	0.050
HLA-A*03	30%	11.1%	8.805	0.003
HLA-A*11	10%	11.3%	0.048	0.827
HLA-B				
HLA-B*07	30%	4.4%	19.882	<0.001
HLA-B*08	10%	3.0%	3.769	0.052
HLA-B*15	10%	2.95%	3.769	0.052
HLA-B*35	20%	16.4%	0.444	0.505
HLA-B*38	20%	6.1%	7.538	0.006
HLA-B*51	10%	9.2%	0.053	0.819

Thus, HLA typing can be used as a screening method to assess an individual's susceptibility to some autoimmune diseases. Furthermore, HLA typing can be used to help assess the prognosis, since it may be involved in the development and progression of the disease (5). The DNA typing analysis of this study revealed an increased rate of HLA-A*01, HLA-A*03, HLA-B*07, and HLA-B*38 alleles in dead cases and a powerful association with the mortality ($P < 0.05$) in our sampled Iranian population.

In conclusion, notwithstanding the prevalence of HLA-A*02 and HLA-B*35 in the normal Iranian population, our results showed that HLA-A*01 and HLA-B*07 were predominant in the death cases. This is the first study examining the HLA pattern in patients with COVID-19 disease in the world. The findings offer evidence that COVID-19 could recognize HLA class I as the receptor on the cell surface. Therefore, people who do not have the abovementioned HLA, are less likely to affect with this virus. Moreover, determining the allele frequency of HLA-A and -B in dead samples could be a good source for other studies in future such as correlations between the alleles and genetic disorders. This study encourages further studies with more samples in other countries.

Conflict of interests

The authors declare that there is no conflict of interests.

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